MEMORANDUM

SUBJECT: Omacide® IPBC: review of a two-generation reproduction study in rats.

EPA Identification Numbers:

P.C. Code: 107801
DP Barcode: D249134
Submissions: S548152
MRID: 44478801
ID# 001258-01219

TO: Adam Heyward / Portia Jenkins
PM Team # 34
Regulatory Management Branch II
Antimicrobials Division (7510W)

FROM: Timothy F. McMahon, Ph.D.
Senior Toxicologist, RASSB
Antimicrobials Division (7510W)

THRU: Laura Morris
Team Leader, Team Two
RASSB/AD (7510W)

And

Norm Cook, Chief
RASSB/AD (7510W)

Registrant: Olin Corporation

Action Requested: Review of a two-generation reproduction study in rats submitted for Omacide® IPBC.

Background

The registrant (Olin Corporation) submitted a two-generation reproduction study on a technical grade of Omacide® IPBC > 97.0 % a.i.). The results of review by the Risk Assessment and Science Support Branch, Antimicrobials Division, is summarized below:

CITATION: Twomey, K. (1996) Omacide® IPBC oral (gavage) rat one-generation reproductive toxicity study (expanded to two generation). Quintiles England Limited, Bromyard Road, Ledbury, Herefordshire, HR8 1LH, England. Report No. OLA/28/95. July, 1996. MRID 44478801. Unpublished.

EXECUTIVE SUMMARY:

Omacide® (IPBC) (>97% a.i.; Batch No. 2DR-293-TSI [labeled G91444-A]) was administered to groups of 25 male and 25 female Crl:CD(SD)BR VAF rats by gavage at doses of 0, 10, 30, or 100 mg/kg/day for two generations (MRID 44478801). F_0 males and females were dosed once daily, by gavage, for 10 weeks prior to mating. Dosing for males continued throughout the mating period and until the day before necropsy. Dosing continued for the females during mating, gestation, and lactation of their litters. Due to the severity of the effects on the F_0 adults and their offspring at 100 mg/kg/day, this dose was discontinued from lactation day 21 and not given to the F_1 adults. Dosing of the F_1 pups selected for breeding began on day 25 post-partum and continued until the animals were approximately 13 weeks of age when they were paired for mating. One litter was produced in the first generation. However, due to a low pregnancy rate in the low-dose group, the F_1 generation animals were remated approximately 2 weeks after their litters had weaned. Dosing for the males continued throughout both mating periods and until the day before necropsy. Dosing continued for the females during the first mating period, pregnancy, and lactation and throughout the second mating period and until the day before necropsy on GD 13. At necropsy, 10 animals/group/sex from each generation were selected for complete microscopic review.

Clinical signs of toxicity observed in the mid- and high dose levels included salivation post-dosing paddling with both forepaws immediately post-dosing ,and hunched posture with the animal holding the abdomen and tail above the cage floor. Post-dosing salivation was listed as a "general" observation for the high-dose F_0 females, but the incidence rate could not be determined from the individual animal data. Salivation post-dosing was also observed in 23/25 mid-dose F_1 females.

No treatment-related effects were observed on body weights, body weight gains, or food con-

sumption for the F_0 males and females and the F_1 males and females throughout the premating interval. Statistically significant differences were sporadic and considered incidental to treatment. For females of both generations, no differences between the treated and control groups were observed for body weights or body weight gains during gestation and lactation and for food consumption during gestation. Food consumption by the high-dose F_0 females was significantly less than the controls during lactation days 1-7 (81% of control; $p \leq 0.01$) and lactation days 7-14 (77% of control; $p \leq 0.001$).

No treatment-related gross findings were observed at necropsy of the F_0 or F_1 females. Microscopic examination of the F_0 adults was unremarkable. In the F_1 adults, diffuse acanthosis with hyperkeratosis was observed in the stomach of 10/10 males and 7/10 females from the 30 mg/kg/day groups.

Therefore, the LOAEL for systemic toxicity is 30 mg/kg/day based on clinical signs of toxicity in the F_0 and F_1 males and females and on microscopic lesions in the stomach of F_1 males and females. The systemic toxicity NOAEL is 10 mg/kg/day.

Fertility indices for the 100 mg/kg/day F_0 male and female animals were significantly ($p \leq 0.05$) less than the controls (80% and 79.2%, respectively, vs 100% and 96%, respectively, for the control groups). No treatment-related effects were observed on copulation or fertility of the F_1 animals.

The live birth indices for the F_1 litters in the 0, 10, 30, and 100 mg/kg/day groups were 97.6%, 98.0%, 90.4%, and 79.5% ($p \leq 0.001$). The live birth index was ≥98% for all groups of F_2 litters. For the F_1 pups, the viability indices on lactation day 4 (precull) were 91.8%, 95.9%, 71.9% ($p \leq 0.01$), and 30.1% ($p \leq 0.001$), respectively, and the cumulative survival indices were 88.3%, 94.0%, 66.6% ($p \leq 0.01$), and 28.2% ($p \leq 0.001$), respectively. For the F_2 pups in the 0, 10, and 30 mg/kg/day groups the viability indices on lactation day 4 (precull) were 92.2%, 96.8%, and 87.2%, respectively, and the cumulative survival indices were 84.7%, 92.8%, and 82.9%, respectively. Whole litter losses occurred for three mid-dose and six high-dose F_0 females and for two mid-dose F_1 females. Clinical signs of toxicity in the pups associated with whole litter losses were indicative of lack of maternal care, such as not being fed or cleaned, being cold, or with abnormal body color.

Body weights of the 100 mg/kg/day F_1 male pups were significantly (79-86% of controls) less than the controls beginning on lactation day 4 (precull) and continuing throughout lactation. Body weights of the 100 mg/kg/day F_1 female pups were significantly (81-93% of controls) less than the controls throughout lactation. Body weight gains by the 100 mg/kg/day F_1 male and female pups were 79% and 82%, respectively, of the control level during lactation days 0-14 and were 93% and 91%, respectively, for lactation days 14-21. Body weights of the 30 mg/kg/day male and female F_1 pups during lactation were slightly but non-significantly lower than the controls. No statistical differences in body weights of the F_2 male pups were observed between the treated and control groups at any time during lactation. F_2 female pups in the 30 mg/kg/day

group had significantly lower body weights than the controls on lactation days 14 (93% of controls; $p \leq 0.05$) and 21 (91% of control; $p \leq 0.001$). Body weight gains by the 30 mg/kg/ F_2 female pups for lactation days 0-14 and 14-21 were 92% and 87%, respectively, of the control level. Pup body weights in the low-dose group were similar to the controls in both generations. Because dosing of the pups did not begin until after weaning at 25 days of age, the only exposure of the pups to the test article was through the milk.

Treatment with the test article resulted in developmental delays of the offspring including a significantly ($p \leq 0.01$) greater anogenital distance in the 30 mg/kg/day F_2 females as compared to the controls (1.1 mm vs 1.0 mm), delayed eye opening for the 100 mg/kg/day F_1 pups (79.2% vs 85.2% of the controls on day 15) and for the 30 mg/kg/day F_2 pups (84.6% vs 96.9% of the controls on day 15).

Therefore, the LOAEL for reproductive toxicity is 30 mg/kg/day based on reduced pup survival, lower pup body weights, and developmental delays during lactation. The reproductive toxicity NOAEL is 10 mg/kg/day.

This study is classified as **Acceptable (guideline)** and satisfies the guideline requirement for a reproduction study (OPPTS 870.3800; 40 CFR §83-4) in rats.

Signed-off 3/3/99 by Norm Cook
TXR# 1001077

DATA EVALUATION REPORT

3-IODO-2-PROPYNYL BUTYLCARBAMATE

STUDY TYPE: MULTIGENERATION REPRODUCTION - RAT (83-4)

Prepared for

Antimicrobials Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 98-259

Primary Reviewer:
Carol S. Forsyth, Ph.D., D.A.B.T. Signature: _____
Date: _____

Secondary Reviewers:
Kowetha A. Davidson, Ph.D., D.A.B.T. Signature: _____
Date: _____

Robert H. Ross, M.S. Group Leader Signature: _____
Date: _____

Quality Assurance:
Eric B. Lewis, M.S. Signature: _____
Date: _____

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under Contract No. DE-AC05-96OR22464.

EPA Reviewer: T. McMahon, Ph.D. _____, Date _____

Senior Toxicologist, RASSB/AD

DATA EVALUATION RECORD

STUDY TYPE: Multigeneration Reproduction - Rat
OPPTS 870.3800 [§83-4]

DP BARCODE: D249134 SUBMISSION: S548152
P.C. CODE: 107801 MRID. NO.: 44478801

TEST MATERIAL (PURITY): Omacide® (IPBC) (>97% a.i.)

SYNONYMS: 3-iodopropynylbutylcarbamate

CITATION: Twomey, K. (1996) Omacide® IPBC oral (gavage) rat one-generation reproductive toxicity study (expanded to two generation). Quintiles England Limited, Bromyard Road, Ledbury, Herefordshire, HR8 1LH, England. Report No. OLA/28/95. July, 1996. MRID 44478801. Unpublished.

SPONSOR: Olin Corporation, 91 Shelton Avenue, P.O. Box 30-9643, New Haven, CT 06511

EXECUTIVE SUMMARY: Omacide® (IPBC) (>97% a.i.; Batch No. 2DR-293-TSI [labeled G91444-A]) was administered to groups of 25 male and 25 female Crl:CD(SD)BR VAF rats by gavage at doses of 0, 10, 30, or 100 mg/kg/day for two generations (MRID 44478801). F_0 males and females were dosed once daily, by gavage, for 10 weeks prior to mating. Dosing for males continued throughout the mating period and until the day before necropsy. Dosing continued for the females during mating, gestation, and lactation of their litters. Due to the severity of the effects on the F_0 adults and their offspring at 100 mg/kg/day, this dose was discontinued from lactation day 21 and not given to the F_1 adults. Dosing of the F_1 pups selected for breeding began on day 25 post-partum and continued until the animals were approximately 13 weeks of age when they were paired for mating. One litter was produced in the first generation. However, due to a low pregnancy rate in the low-dose group, the F_1 generation animals were remated approximately 2 weeks after their litters had weaned. Dosing for the males continued throughout both mating periods and until the day before necropsy. Dosing continued for the females during the first mating period, pregnancy, and lactation and throughout the second mating period and until the day before necropsy on GD 13. At necropsy, 10 animals/group/sex from each generation were selected for complete microscopic review.

Clinical signs of toxicity observed in the mid- and high dose levels included salivation post-dosing paddling with both forepaws immediately post-dosing ,and hunched posture with the animal holding the abdomen and tail above the cage floor. Post-dosing salivation was listed as a "general" observation for the high-dose F_0 females, but the incidence rate could not be determined from the individual animal data. Salivation post-dosing was also observed in 23/25 mid-dose F_1 females.

No treatment-related effects were observed on body weights, body weight gains, or food consumption for the F_0 males and females and the F_1 males and females throughout the premating interval. Statistically significant differences were sporadic and considered incidental to treatment. For females of both generations, no differences between the treated and control groups were observed for body weights or body weight gains during gestation and lactation and for food consumption during gestation. Food consumption by the high-dose F_0 females was significantly less than the controls during lactation days 1-7 (81% of control; $p \leq 0.01$) and lactation days 7-14 (77% of control; $p \leq 0.001$).

No treatment-related gross findings were observed at necropsy of the F_0 or F_1 females. Microscopic examination of the F_0 adults was unremarkable. In the F_1 adults, diffuse acanthosis with hyperkeratosis was observed in the stomach of 10/10 males and 7/10 females from the 30 mg/kg/day groups.

Therefore, the LOAEL for systemic toxicity is 30 mg/kg/day based on clinical signs of toxicity in the F_0 and F_1 males and females and on microscopic lesions in the stomach of F_1 males and females. The systemic toxicity NOAEL is 10 mg/kg/day.

Fertility indices for the 100 mg/kg/day F_0 male and female animals were significantly ($p \leq 0.05$) less than the controls (80% and 79.2%, respectively, vs 100% and 96%, respectively, for the control groups). No treatment-related effects were observed on copulation or fertility of the F_1 animals.

The live birth indices for the F_1 litters in the 0, 10, 30, and 100 mg/kg/day groups were 97.6%, 98.0%, 90.4%, and 79.5% ($p \leq 0.001$). The live birth index was ≥98% for all groups of F_2 litters. For the F_1 pups, the viability indices on lactation day 4 (precull) were 91.8%, 95.9%, 71.9% ($p \leq 0.01$), and 30.1% ($p \leq 0.001$), respectively, and the cumulative survival indices were 88.3%, 94.0%, 66.6% ($p \leq 0.01$), and 28.2% ($p \leq 0.001$), respectively. For the F_2 pups in the 0, 10, and 30 mg/kg/day groups the viability indices on lactation day 4 (precull) were 92.2%, 96.8%, and 87.2%, respectively, and the cumulative survival indices were 84.7%, 92.8%, and 82.9%, respectively. Whole litter losses occurred for three mid-dose and six high-dose F_0 females and for two mid-dose F_1 females. Clinical signs of toxicity in the pups associated with whole litter losses were indicative of lack of maternal care, such as not being fed or cleaned, being cold, or with abnormal body color.

Body weights of the 100 mg/kg/day F_1 male pups were significantly (79-86% of controls) less than the controls beginning on lactation day 4 (precull) and continuing throughout lactation. Body weights of the 100 mg/kg/day F_1 female pups were significantly (81-93% of controls) less than the controls throughout lactation. Body weight gains by the 100 mg/kg/day F_1 male and female pups were 79% and 82%, respectively, of the control level during lactation days 0-14 and were 93% and 91%, respectively, for lactation days 14-21. Body weights of the 30 mg/kg/day male and female F_1 pups during lactation were slightly but non-significantly lower than the controls. No statistical differences in body weights of the F_2 male pups were observed between the treated and control groups at any time during lactation. F_2 female pups in the 30 mg/kg/day group had significantly lower body weights than the controls on lactation days 14 (93% of

controls; $p \leq 0.05$) and 21 (91% of control; $p \leq 0.001$). Body weight gains by the 30 mg/kg/ F_2 female pups for lactation days 0-14 and 14-21 were 92% and 87%, respectively, of the control level. Pup body weights in the low-dose group were similar to the controls in both generations. Because dosing of the pups did not begin until after weaning at 25 days of age, the only exposure of the pups to the test article was through the milk.

Treatment with the test article resulted in developmental delays of the offspring including a significantly ($p \leq 0.01$) greater anogenital distance in the 30 mg/kg/day F_2 females as compared to the controls (1.1 mm vs 1.0 mm), delayed eye opening for the 100 mg/kg/day F_1 pups (79.2% vs 85.2% of the controls on day 15) and for the 30 mg/kg/day F_2 pups (84.6% vs 96.9% of the controls on day 15).

Therefore, the LOAEL for reproductive toxicity is 30 mg/kg/day based on reduced pup survival, lower pup body weights, and developmental delays during lactation. The reproductive toxicity NOAEL is 10 mg/kg/day.

This study is classified as **Acceptable (guideline)** and satisfies the guideline requirement for a reproduction study (OPPTS 870.3800; 40 CFR §83-4) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Omacide® (IPBC)

   Description: off-white, coarse powder
   Batch No.: 2DR-293-TSI (labeled G91444-A)
   Purity: >97% a.i.
   Stability of compound: not stated
   CAS No.: 55406-53-6
   Structure: not given

2. Vehicle and/or positive control

   Methylcellulose was used as the vehicle and negative control. No positive control was used in this study. Doses were given in a volume of 10 mL/kg based on the most recently recorded body weight.

3. Test animals

Species: Rat
Strain: Crl:CD(SD)BR VAF
Age and weight at start of study: 5-7 weeks; males: 253-300 g; females: 139-170 g
Source: Charles River (U.K.) Ltd., Margate, England
Housing: Animals were housed 5/cage by sex in grid bottomed cages during the premating period. During gestation and lactation, females were individually housed in solid bottomed polypropylene cages containing sawdust as bedding material.
Diet: SQC Rat and Mouse No. 3 Breeder pelleted rodent diet from Special Diets Services, Witham, Essex, U.K. was available *ad libitum*.
Water: Mains tap water was available *ad libitum*.
Environmental conditions:
Temperature: 22 ± 3°C
Humidity: 50 ± 20%
Air Changes: 16/hour
Photoperiod: 12 hour light/12 hour dark
Acclimation period: 10 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates

Start: October 10, 1994; end: July 7, 1995

2. Mating procedure

For mating, females were paired with a male from the same dose group for 7 days or until positive evidence of mating was observed. Positive evidence of mating was confirmed by the presence of sperm in a vaginal smear. If evidence of mating was not detected after 7 days, the female was paired for up to an additional 14 days with a different male from the same dose group that had previously mated. Non-mated males were paired for up to a further 14 days with one of the untreated females retained for test-matings. The F_1 adults were randomly selected from the F_1 litters. One litter was produced by each generation. Due to a low pregnancy rate in the 10 mg/kg F1 females (60%), re-mating occurred approximately 2 weeks after weaning of the first litter. Pregnant females which were part of the re-mating were killed on day 13 of pregnancy. For the second mating in the F_1 generation, if evidence of mating was not detected after 7 days, the female was paired for up to an additional 7 days with a different male from the same dose group. Day 0 of gestation was designated as the day evidence of mating was observed. Day 0 of lactation was the day on which delivery of pups was completed.

3. Study schedule

F_0 males and females were dosed once daily, by gavage, for 10 weeks prior to mating. Dosing for males continued throughout the mating period and until the day before necropsy. Dosing continued for the females during mating, gestation, and lactation of their litters. Due to the severity of effects at 100 mg/kg/day on the F_0 adults and their offspring (decreased pup survival during lactation, lack of maternal care of the F_1 pups, premature sacrifice of four F_0 females due to difficult parturition), this dose group was discontinued on day 21 post-partum. Dosing of the F_1 pups selected for breeding began on day 25 post-partum and continued until the animals were approximately 13 weeks of age when they were paired for mating. Due to a low pregnancy rate in the low-dose group, the F_1 generation animals were remated approximately 2 weeks after their litters had weaned. Dosing for the males continued throughout both mating periods and until the day before necropsy. Dosing continued for the females during the first mating period, pregnancy, and lactation and throughout the second mating period and until the day before necropsy on GD 13.

4. Animal assignment

F_0 parental animals were assigned to groups based on computer randomization using a body weight stratification technique. The F_1 generation weanling pups were randomly selected by litter. Due to the severity of the effects on the F_0 adults and their offspring, dosing for the high-dose group was discontinued from lactation day 21. Additional untreated or control females from each generation were retained for test mating males that had no confirmed mating with the original study female. Animal assignment is given in Table 1.

Table 1. Animal assignment

Dose group	Dosage (mg/kg/day)	No. of parental animals per group			
		F_0 Generation		F_1 Generation	
		Male	Female	Male	Female
0 (Control)	0	25	25	25	25
1 (Low)	10	25	25	25	25
2 (Mid)	30	25	25	25	25
4 (High)	100	25	25	–	–

Data taken from text tables pp. 22 and 23, MRID 44478801.

5. Dose selection rationale

Dose levels were selected based on the results of a preliminary range-finding study and previously performed toxicity studies. Details of these studies were not provided.

6. Dose solution preparation and analysis

Dosing solutions were prepared weekly as suspensions in 1% aqueous methylcellulose and separate formulations were prepared for each dose level. For each dose level, the weighed amount of test article was suspended in the appropriate quantity of vehicle. The dosing solutions were divided into aliquots and stored at 4°C in the dark until used. Aliquots were allowed to stand at room temperature for approximately 1 hour before being used and were continuously mixed with a magnetic stirrer during dosing. On weeks 1, 5, 10, 15, 20, 25, 30, and 35, samples from each dose preparation were taken and analyzed for concentration. The stability of aqueous suspensions of the test article prepared at the low and high concentrations was assessed in a study conducted previously by the testing facility. Samples were analyzed for concentration after storage at 4°C for 0, 1, 2, 4, or 8 days. Homogeneity had also been determined in a prior study on samples taken from the top, middle, and bottom of the 10 and 100 mg/kg/day solutions.

Results –
Homogeneity analysis: Concentrations of the test article from the top, middle, and bottom of low- and high-dose solutions ranged from 95-103% and 90-110%, respectively, of nominal.

Stability analysis: After storage from up to 8 days, the concentrations of test article in the low and high-dose solutions ranged from 92-108% and 95-108%, respectively, of their initial measured concentrations.

Concentration analysis: Throughout the study, concentrations of the 10, 30, and 100 mg/kg/day dosing solutions ranged from 87-108%, 88-108%, and 90-98%, respectively, of nominal with the exception of week 15. Repeated analyses of the dosing solutions prepared for week 15 showed concentrations of 80-86%, 81-90%, and 78-90%, respectively, of nominal.

Results of the analyses show that the test article was adequately mixed with the dosing vehicle, was stable under the conditions of this study, and that the actual dosages to the animals were within an acceptable range with the exception of week 15. Lower than expected measured concentrations for this one week are not considered to affect the integrity of this study.

C. OBSERVATIONS

1. Parental animals

All animals were observed twice daily for mortality and moribundity and once daily for clinical signs of toxicity. Body weights of the F_0 adults were recorded weekly during the premating period. Body weights of the F_1 adults were recorded on day 25 post-partum and daily until day 32 post-partum, after which they were recorded weekly. Females were weighed daily from the start of mating, however, only body weights on GD 0, 7, 14, and 20 and lactation days 1, 7, 14, and 21 were reported. Food consumption for all adults was measured weekly during the premating period. Food consumption for females was measured weekly during gestation and for the first two weeks of lactation. Food efficiency was not calculated.

Vaginal smears were taken daily from each female for three weeks before the start of the mating periods (except for prior to the second F_1 mating), and during each mating period until confirmation of mating or until the end of the mating period. The smears were examined by light microscopy and the stage of the estrous cycle determined by the type of cell present.

At necropsy, sperm samples were collected from one cauda epididymides from all males for evaluation of total number, motility, and morphology.

2. Litter observations

Litter observations were made as shown in Table 2. All females were allowed to litter naturally. The day parturition was complete was lactation day 0 and litter size and pup sexes were determined as soon as possible after birth and daily thereafter. Pups were weighed on lactation days 0, 4, 7, 14, and 21. On lactation day 4, litters were randomly culled to 4 pups per sex, where possible. All culled pups and offspring found dead were necropsied. Pups were weaned on lactation day 21.

The anogenital distance was recorded for all live pups on lactation day 0. Additionally, the following developmental milestones were recorded: ears open (pups/litter on lactation day 3), eyes open (pups/litter on lactation day 15), static righting reflex on day 5, startle response on day 15, and pupillary light reflex on day 21. Beginning on day 35 post-partum, all males were examined for preputial separation and beginning on day 28 post-partum, all females were examined for vaginal perforation.

TABLE 2. F_1 and F_2 Litter observations

Observation	Lactation day				
	Day 0	Day 4	Day 7	Day 14	Day 21

Dead/moribund pups	Daily				
No. pups	Daily				
Pup weight	X	X[a]	X	X	X
Sex of each pup	Daily				
Clinical signs	Daily				

[a]Pre- and post-cull.

3. Postmortem observations

a. Parental animals

F_0 males were killed two weeks after the end of the mating period. F_1 males were killed at the end of the second mating period. F_0 females were sacrificed following weaning of their pups on lactation day 21. F_1 females were killed on GD 13 following the second mating period. Non-mated and non-pregnant F_0 and F_1 females were killed after their nulliparous state was confirmed by palpation. All animals were killed by CO_2 asphyxiation. A gross necropsy was performed on all surviving adults and on adults that died or were sacrificed moribund during the study. Tissues from the following (X) organs were preserved in neutral buffered formaldehyde with the exception of the testes which were fixed in Bouin's solution and then transferred to neutral buffered formaldehyde. The (XX) tissues were weighed. Organs from the control and high-dose animals and any animals that failed to sire or conceive were examined histopathologically. Additionally, 10 rats/sex from the control and high-dose groups of each generation were selected for complete microscopic review.
Immediately after weighing, one of the cauda epidiymides from all males were used for sperm examination. Sperm concentration and sperm motility were assessed using a computer assisted sperm motility analysis technology. Sperm morphology were examined by light microscopy, which included examination for broken, decapitate, and two-headed sperm, tail abnormalities and other gross defects.

X	Testes	X	Ovaries
X	Epididymides	X	Uterus
X	Prostate	X	Vagina
X	Seminal vesicles	X	Cervix
X	Coagulating gland	X	Oviducts
X	Gross lesions	X	Pituitary
X	Liver	X	
X		X	
X			
X			

X X			

b. Offspring

Pups found dead or killed moribund before weaning were subjected to a gross necropsy. Culled pups, F_1 pups not selected for mating, and all F_2 weanlings were examined grossly. Pups up to 14 days old were killed by intracardiac injection of sodium pentobarbitone and older pups were killed by CO_2 asphyxiation. Gross lesions were removed and fixed in neutral buffered formaldehyde.

D. DATA ANALYSIS

1. Statistical analyses

For interval data, group means and standard deviations were calculated for each observation time. These data included parental and pup body weights, parental food consumption, parental and pup organ weights, and pup anogenital distances. Analysis of variance (ANOVA) was performed on all parameters and Levene's test was used to examine heterogeneity of variance. If Levene's test was not significant, William's test was used to compare the treated groups to the control group. If Levene's test was significant, then the Kruskal-Wallis test followed by Shirley's non-parametric version of William's test was used to determine differences between the treated groups. Data for which Levene's test was significant included estrous cycle duration, sperm number and motility data, duration of gestation, number of pups born, litter indices, percentages of pups with developmental variations, and pup sex ratios. Fisher's Exact Test was used to analyze copulation index, fertility index, and gestation index data.

2. Indices

Reproductive indices: Males were considered fertile if they sired a litter while females were considered fertile if they became pregnant. The following reproductive indices were calculated:

Copulation index (%) = (No. animals mated/No. animals paired) × 100

Fertility index (%) = (No. animals fertile/No. animals mated) × 100

Offspring viability indices: The day of birth was designated as day 0 of lactation. The following offspring viability indices were calculated:

Gestation index (%) = (No. litters with live young/No. pregnant females) × 100

Live birth index (%) = (No. pups born alive/No. pups born) × 100

Viability index 1 (%) = (No. pups alive on day 4 [precull]/No. pups born live) × 100

Viability index 2 (%) = (No. pups alive on day 14/No. pups alive on day 4 [postcull]) × 100

Viability index 3 (%) = (No. pups alive on day 21/No. pups alive on day 14) × 100

Cumulative survival index (%) = (No. pups alive on day 21/No. pups alive on day 4 [postcull]) × (No. pups alive on day 4 [precull]/No. pups born) × 100

Sex ratio of each litter = (No. male or female pups born/No. pups born) × 100

3. Historical control data were included for comparison with concurrent controls.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs

All F_0 and F_1 males survived to scheduled sacrifice. One mid-dose and 4 high-dose F_0 females were sacrificed *in extremis* with dystocia. Another high-dose female was sacrificed moribund after the observations of piloerection, pale appearance, hunched posture, and hypoactive behavior; this animal had a hard mass with ulceration and scabbing on its right forelimb. One control F_1 female was observed to have a hole in the upper palate due to excessively long lower incisors soon after selection; this animal was removed from the study and replaced. Another control female was sacrificed *in extremis* and diagnosed with a fibroadenoma. One low-dose F_1 female

was found dead with no previous signs and two mid-dose F_1 females were sacrificed moribund following the observations of emaciation, hunched posture, piloerection, irregular breathing, and/or unsteady gait. The cause of death or moribund condition was not identified for the low- and mid-dose animals.

Clinical signs of toxicity are listed in Table 3. In the F_0 males and females treatment-related clinical signs of toxicity in the mid- and high-dose groups included salivation post-dosing, paddling with both forepaws immediately post-dosing, and hunched posture with the animal holding the abdomen and tail above the cage floor. Post-dosing salivation was listed as a "general" observation for the high-dose F_0 females, but the incidence rate could not be determined from the individual animal data. In the F_1 animals, salivation and paddling with both forepaws immediately post-dosing was observed in mid-dose males and females. Ridges on the tails of the F_1 animals were observed in all groups, including the control. Hair loss and minor scabbing were a common finding in males and females of both generations.

TABLE 3: Incidence rate of clinical signs of toxicity in rats administered Omacide® (IPBC) for two generations

Observation	0 mg/kg/d	10 mg/kg/d	30 mg/kg/d	100 mg/kg/d	0 mg/kg/d	10 mg/kg/d	30 mg/kg/d	100 mg/kg/d
	Males				Females			
	F_0 Adults							
Salivation	0/25	0/25	25/25	25/25	0/25	0/25	5/25	-[a]
Hunched	0/25	0/25	25/25	25/25	0/25	0/25	0/25	25/25
Paddling with forepaws	0/25	0/25	25/25	25/25	0/25	0/25	25/25	25/25
	F_1 Adults							
Salivation	0/25	0/25	25/25	n/a	0/25	0/25	23/25	n/a
Paddling with forepaws	0/25	0/25	25/25	n/a	0/25	0/25	25/25	n/a

Data taken from Appendices 1, 2, 24, and 25, pp. 167-171, 172-178, 371-380, and 381-393, respectively, MRID 44478801.
[a]Incidence rate could not be determined; "general" observation.
n/a = not applicable; F_1 adults were not given 100 mg/kg/day.

2. Body weight and food consumption

a. Premating

Body weight and food consumption data for the F_0 males during the premating period are given in Table 4. No statistically significant differences were observed between the treated and control groups in mean body weights at any time during

the study. Body weights, body weight gains, and food consumption for the low- and mid-dose groups were similar to the control group values throughout the premating interval. Body weight gain in the high-dose F_0 males was decreased 4% on day 8 pre-mating and was identified as statistically significant ($p < 0.05$ vs control). Overall weight gain for high dose F_0 males was decreased by 11% vs control. Food consumption in high-dose F_0 males was decreased by 8% during the first week of pre-mating, but thereafter was similar to controls.

Body weight and food consumption data for the F_0 females during the premating period are given in Table 5. No treatment-related differences in body weights, body weight gains, or food consumption were observed between the treated and control groups at any time during the premating interval. Body weight gain by the high-dose group during week 8 was significantly ($p \leq 0.05$) less than the control group, but there was no dose- or time-related pattern.

Table 4. F_0 males: mean body weights and food consumption during the premating period

	Treatment group			
Day of study	**0 mg/kg/day**	**10 mg/kg/day**	**30 mg/kg/day**	**100 mg/kg/day**
Body weight (g)				
Day 1	276	275	277	276
Day 8	328	331	332	317
Day 22	407	407	412	396
Day 43	491	490	494	472
Day 57	531	532	537	510
Day 71 (end of premating)	570	571	577	542
Day 106 (end of study)	625	628	632	588
Overall weight gain premating[a]	294	296	300	266
Overall weight gain[a]	349	353	355	312
Week of Study	**Food consumption prior to mating (g/rat/day)**			
Week 1	33.3	33.4	33.6	30.7*
Week 2	32.8	32.7	33.2	32.0
Week 5	33.5	33.7	35.0	34.5
Week 8	36.2	36.7	38.7	37.2
Week 10	32.8	33.8	34.6	32.4

Data taken from Tables 1 and 5, pp. 122 and 128, respectively, MRID 44478801.
[a]Calculated by reviewer.

Significantly different from control; *p ≤ 0.05.

Table 5. F_0 Females: mean body weights and food consumption during the premating period

Day of study	Treatment group			
	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Body weight (g)				
Day 1	152	153	153	152
Day 8	183	184	185	183
Day 22	232	235	239	232
Day 43	279	285	287	276
Day 57	305	309	311	297
Day 71 (end of premating)	323	328	330	313
Overall weight gain premating[a]	171	175	177	161
Week of Study	**Food consumption (g/rat/day)**			
Week 1	21.3	21.7	21.3	21.9
Week 2	22.9	23.0	23.9	23.5
Week 5	24.9	24.3	26.5	25.0
Week 8	28.4	27.1	28.4	27.0
Week 10	24.1	23.8	25.8	25.1

Data taken from Tables 2a and 6a, pp. 123 and 129, respectively, MRID 44478801.
[a]Calculated by reviewer.

Body weight and food consumption data for the adult F_1 males during the premating period are given in Table 6. Body weights, body weight gains, and food consumption for the treated groups were comparable to the controls throughout the study. Body weight gains by the mid-dose group were occasionally significantly less than or greater than the controls. Food consumption by the treated groups was significantly ($p \leq 0.05$) greater than the control group during week 24 of the study.

Body weight and food consumption data for the adult F_1 females during the premating period are given in Table 7. Body weights, body weight gains, and food consumption for the treated groups were comparable to the controls throughout the premating interval.

TABLE 6. F_1 males: Mean body weights and food consumption during the premating period

Days of age	Treatment group		
	0 mg/kg/day	**10 mg/kg/day**	**30 mg/kg/day**
Body weight (g)			
25	78	78	78
32	125	127	121
53	308	317	312
74	442	455	451
95 (end of premating)	515	534	534
165 (end of study)	607	630	628
Overall weight gain premating[a]	437	456	456
Overall weight gain[a]	529	552	550
Week of Study	**Food consumption (g/rat/day)**		
Week 19	23.2	24.6	23.6
Week 20	27.4	28.7	28.8
Week 22	36.0	36.1	37.5
Week 24	37.0	39.0*	39.5*
Week 27	36.0	37.0	36.6

Data taken from Tables 15 and 19, pp. 139 and 146, respectively, MRID 44478801.
[a]Calculated by reviewer.
Significantly different from control; *$p \leq 0.05$.

TABLE 7. F_1 Females: Mean body weights and food consumption during the premating period

Days of age	Treatment group		
	0 mg/kg/day	**10 mg/kg/day**	**30 mg/kg/day**
Body weight (g)			
25	76	75	73
32	118	116	111
53	225	231	224
74	289	297	286
95	333	337	325
Overall weight gain premating[a]	257	262	252
Week of Study	**Food consumption (g/rat/day)**		
Week 19	21.0	21.3	21.1
Week 20	23.9	23.1	23.5
Week 22	25.6	27.1	27.5
Week 24	28.6	30.2	29.6
Week 27	28.2	27.7	28.4

Data taken from Tables 16a and 20a, pp. 140 and 147, respectively, MRID 44478801.
[a]Calculated by reviewer.

b. Gestation and lactation

Body weights and food consumption data for the F_0 and F_1 adult females during gestation and lactation are given in Tables 8 and 9, respectively. For both generations, no differences between the treated and control groups were observed for body weights or body weight gains during gestation and lactation and for food consumption during gestation. Food consumption by the high-dose F_0 females was significantly less than the controls during lactation days 1-7 (81% of control; $p \leq 0.01$) and lactation days 7-14 (77% of control; $p \leq 0.001$).

TABLE 8. F_0 Females: Selected mean body weights and food consumption during gestation and lactation

Observation	Treatment group			
	0 mg/kg/day	**10 mg/kg/day**	**30 mg/kg/day**	**100 mg/kg/day**
Mean body weight (g)				
Day 0 of gestation	321	326	327	312
Day 20 of gestation	459	462	470	450
Day 1 of lactation	339	342	340	333
Day 21 of lactation	373	383	380	373
Mean food consumption (g/rat/day)				
Day 0-7 of gestation	26.1	25.9	26.1	25.7
Day 14-20 of gestation	31.1	30.7	31.8	30.4
Day 1-7 of lactation	39.8	39.6	38.7	32.1** (81)[a]
Day 7-14 of lactation	67.7	70.2	66.4	52.4*** (77)

Data taken from Tables 2b and 6b, pp. 124 and 130 respectively, MRID 44478801.
[a]Numbers in parentheses are per cent of control.
Significantly different from control; **$p \leq 0.01$, ***$p \leq 0.001$.

TABLE 9. F_1 Females: Selected mean body weights and food consumption during gestation and lactation

Observation	Treatment group		
	0 mg/kg/day	**10 mg/kg/day**	**30 mg/kg/day**
F_{2a} Litters			
Mean body weight (g)			
Day 0 of gestation	334	325	324
Day 20 of gestation	482	472	476
Day 1 of lactation	372	365	358
Day 21 of lactation	396	388	386
Mean food consumption (g/rat/day)			
Day 0-7 of gestation	27.0	26.1	27.6
Day 14-20 of gestation	33.5	32.5	34.5
Day 1-7 of lactation	38.5	37.2	37.8
Day 7-14 of lactation	63.1	61.3	62.1
F_{2b} Litters[a]			
Mean body weight (g)			
Day 0 of gestation	373	377	359
Day 13 of gestation	424	424	410
Mean food consumption (g/rat/day)			
Day 0-7 of gestation	33.1	33.8	33.8
Day 7-13 of gestation	33.6	34.5	34.3

Data taken from Tables 16b, 16c, 20b, and 20c, pp. 141, 142, 148, and 149, respectively, MRID 44478801.
[a]Dams were killed on GD 13.

3. Reproductive function

a. Estrous cycle length or periodicity - The report stated that no differences were observed between the treated and control groups in the mean number of estrous cycles during the three weeks prior to mating for either the F_0 or F_1 females. However, only individual animal data (Appendix 9a and Apendix 33a) were presented. These data appear to show no significant differences in estrous cycle duration.

b. Sperm measures - Cauda epididymal sperm evaluation showed no differences in sperm motility, concentration, or morphology between the treated and control groups of either generation.Summary data were not provided in the report.

c. Sexual maturation of the offspring - In F_1 males, the average day on which preputial separation was observed in the 0, 10, and 30 mg/kg/day groups was 45.1, 45.6, and 45.7, respectively. For F_1 females, vaginal perforation was observed by day 36.1, 37.2, and 37.4, respectively.

4. Reproductive performance

The reproductive performances of the F_0 and F_1 animals are summarized in Tables 10 and 11, respectively. The mean length of gestation was significantly ($p \leq 0.05$ or 0.01) longer in all treated F_0 groups as compared to the control. Fertility indices for the high-dose F_0 male and female animals were significantly ($p \leq 0.05$) less than the controls. The copulation index for the high-dose F_0 males was slightly lower than the controls, however, all animals except one mated when placed with a test-mate female.

No treatment-related effects were observed on copulation or fertility of the F_1 animals. For the first pairing, the copulation indices for the treated males were slightly lower than the controls, however, all animals mated with test-mate females. Due to unexplained low fertility indices for the low-dose males and females, a second pairing was conducted. After the second pairing, fertility indices were similar between the treated and control groups.

TABLE 10. Reproductive performance of the F_0 adults

Observation	**0 mg/kg/day**	**10 mg/kg/day**	**30 mg/kg/day**	**100 mg/kg/day**
Number males mated	24	21	24	20
Number females mated	25	25	25	24
Number males fertile	24	21	24	16
Number females pregnant	24	24	24	19
Mean precoital interval (days)	3.0	3.5	3.4	3.8
Mean gestation length (days)	21.7	21.9*	22.0**	22.0*
Male copulation index (%)	96	84	96	80
Female copulation index (%)	100	100	100	96
Male fertility index (%)	100	100	96	80*
Female fertility index (%)	96	96	96	79.2*

Data taken from Tables 7, 8, and 9, pp. 131, 132, and 133, respectively, MRID 44478801.
Significantly different from control: *$p \leq 0.05$; **$p \leq 0.01$.

TABLE 11. Reproductive performance of the F_1 adults

Observation	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day
First pairing			
Number males mated	22	18	20
Number females mated	24	23	24
Number males fertile	21	14	18
Number females pregnant	21	14	22
Mean precoital interval (days)	2.8	4.6	3.8
Mean gestation length (days)	21.8	21.9	21.9
Male copulation index (%)	88.0	72.0	75.0
Female copulation index (%)	96.0	92.0	96.0
Male fertility index (%)	95.5	77.8	90.0
Female fertility index (%)	87.5	60.1	91.7
Second pairing			
Number males mated	21	17	20
Number females mated	23	20	21
Number males fertile	20	15	18
Number females pregnant	20	17	19
Mean precoital interval (days)	3.5	4.1	3.4
Mean gestation length (days)	n/a	n/a	n/a
Male copulation index (%)	84.0	68.0	90.9
Female copulation index (%)	95.8	83.3	91.3
Male fertility index (%)	95.2	88.2	90.0
Female fertility index (%)	86.9	85.0	90.5

Data taken from Tables 22a, 22b, 23a, 23b, and 24a, pp. 151, 152, 153, 154, and 155, respectively, MRID 44478801.

5. Parental postmortem results

a. Organ weights

Absolute organ weights from the treated F_0 males were similar to the control group. Organ-to-body weight ratios of the seminal vesicles, liver, epididymides, and testes from the high-dose F_0 males were increased by 10%, 16%, 10%, and 9% respectively, probably as a result of the slightly lower terminal body weights of the high-dose group. Absolute liver weights from the mid- and high-dose F_0 females were by contrast decreased approximately 10% vs control ($p \leq 0.05$ and 0.01 for mid- and high-dose females respectively) . Absolute and relative ovarian weights were increased in high-dose F_0 females (15% and 22% increase, respectively).

Absolute organ weights from the treated F_1 males and females were similar to their respective control groups. Relative heart weights from the low- and mid-dose F_1 males were significantly ($p \leq 0.05$) less than the controls. Absolute ovarian weight was decreased by 7% and relative ovarian by 6% in the low- and mid-dose F_1 females vs. controls. The decrease in ovarian weight observed for the F_1 females in relation to the increase in ovarian weight for the F_0 females is not readily explained.

b. Pathology

1. Macroscopic pathology

No treatment-related findings were observed at necropsy of F_0 or F_1 females.

2. Microscopic pathology

Histological lesions were not reported for the F_0 animals, although gross abnormalities were summarized in Appendix 15 of the report; therefore, the reviewer assumes that no treatment-related microscopic abnormalities were observed. In the F_1 adults, diffuse acanthosis with hyperkeratosis was observed in the stomach of 10/10 males and 7/10 females from the 30 mg/kg/day groups.

B. OFFSPRING

1. Viability and clinical signs

Viability data for the F_1 and F_2 litters are given in Table 12. Pup deaths were increased at 30 and 100 mg/kg/day particularly during the first four days of lactation. The mean live birth index, viability index on day 4, and the cumulative survival index for the high-dose F_1 litters were significantly lower than the controls. The mid-dose F_1 litters also had significantly lower viability on day 4 (viability index 1) and cumulative survival indices. Whole litter losses occurred for 3 mid-dose and 6 high-dose F_0 females. Clinical signs of toxicity associated with whole litter losses were indicative of lack of maternal care, such as not being fed or cleaned, being cold, or with abnormal body color. Viability and survival of the F_2 litters was slightly (n.s.)

reduced in the mid-dose group and two dams had whole litter loss. Mean litter sizes at birth and pup sex ratios were similar between the treated and control groups of both generations.

TABLE 12. Viability of F_1 and F_{2a} litters during lactation

Observation/study time	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
F_1 litters				
Number of litters	24	24	24	15
Whole litter losses	0	0	3	6
Per cent male pups	49	52	53	50
Mean litter size on day 0	15.1	14.7	15.7	14.9
Live birth index (%)	97.6	98.0	90.4	79.5***
Viability index 1 (%)	91.8	95.9	71.9**	30.1***
Viability index 2 (%)	99.0	100.0	94.0	100.0
Viability index 3 (%)	99.5	100.0	100.0	100.0
Cumulative survival index (%)	88.3	94.0	66.6**	28.2***
F_{2a} litters				
Number of litters	21	14	22	-
Whole litter losses	0	0	2	-
Per cent male pups	50	45	49	-
Mean litter size on day 0	15.1	13.9	15.5	-
Live birth index (%)	98.2	98.1	98.0	-
Viability index 1 (%)	92.2	96.8	87.2	-
Viability index 2 (%)	92.9	97.3	98.1	-
Viability index 3 (%)	99.0	100.0	100.0	-
Cumulative survival index (%)	84.7	92.8	82.9	-

Data taken from Tables 9 and 24a, pp. 133 and 155, respectively, MRID 44478801.
Significantly different from control; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

2. Body weight

Selected body weights and body weight gains of the F_1 and F_{2a} pups during lactation are given in Tables 13 and 14, respectively. Body weights of the high-dose F_1 male pups were significantly (79-86% of controls) less than the controls beginning on lactation day 4 (precull) and continuing throughout lactation. Body weights of the high-dose F_1 female pups were significantly (81-93% of controls) less than the controls at birth and throughout lactation. Body weight gains by the high-dose F_1 male and female pups were 79% and 82%, respectively, of the control level during lactation days 0-14 and were 93% and 91%, respectively, for lactation days 14-21.

Body weights of the mid-dose male and female F_1 pups were slightly (n.s) lower than the controls with weight gains during lactation 95-98% of the controls. No statistical differences in body weights of the F_2 male pups were observed between the treated and control groups at any time during lactation; however, body weights of the mid-dose males were slightly lower than the controls throughout. Mid-dose F_2 female pups had significantly lower body weights than the controls on lactation days 14 (93% of controls; $p \leq 0.05$) and 21 (91% of control; $p \leq 0.001$). Body weight gains by the mid-dose F_2 female pups for lactation days 0-14 and 14-21 were 92% and 87%, respectively, of the control level. Pup body weights in the low-dose group were similar to the controls in both generations.

TABLE 13. Mean pup body weights and body weight gains of F_1 litters during lactation (g)

Day of lactation	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Males				
Day 0	6.2	6.3	6.1	5.9
Day 4 (precull)	9.9	9.8	9.6	8.2** (83)[a]
Day 7	16.5	16.8	15.8	13.0*** (79)
Day 14	35.6	35.7	33.9	29.1*** (82)
Day 21	57.7	57.8	55.5	49.7*** (86)
Wt. gain days 0-14[b]	29.4	29.4	27.8 (95)	23.2 (79)
Wt. gain days 14-21[b]	22.1	22.1	21.6 (98)	20.6 (93)
Females				
Day 0	5.9	5.9	5.8	5.5* (93)
Day 4 (precull)	9.6	9.3	9.1	8.3* (86)
Day 7	16.1	15.9	15.3	13.0*** (81)
Day 14	34.4	34.0	33.1	28.9*** (84)
Day 21	55.9	55.0	53.9	48.4*** (87)
Wt. gain days 0-14[b]	28.5	28.1	27.3 (95)	23.4 (82)
Wt. gain days 14-21[b]	21.5	21.0	20.8 (97)	19.5 (91)

Data taken from Table 12, p. 136, MRID 44478801.
[a]Number in parentheses is per cent of control.
[b]Calculated by reviewer.
Significantly different from controls; *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

TABLE 14. Mean pup body weights and body weight gains of F_{2a} litters during lactation (g)

TABLE 14. Mean pup body weights and body weight gains of F_{2a} litters during lactation (g)

Day of lactation	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Males			
Day 0	6.4	6.3	6.3
Day 4 (precull)	9.2	9.7	9.1
Day 7	15.0	16.2	14.8
Day 14	34.4	35.1	32.7
Day 21	56.3	56.9	53.4
Wt. gain days 0-14[b]	28.0	28.8	26.4 (94)[a]
Wt. gain days 14-21[b]	21.9	21.8	20.7 (95)
Females			
Day 0	6.0	6.0	5.9
Day 4 (precull)	8.8	9.3	8.7
Day 7	14.5	15.4	14.2
Day 14	33.8	33.9	31.4* (93)
Day 21	55.9	55.6	50.7*** (91)
Wt. gain days 0-14[b]	27.8	27.9	25.5 (92)
Wt. gain days 14-21[b]	22.1	21.7	19.3 (87)

Data taken from Table 29, p. 161, MRID 44478801.
[a]Number in parentheses is per cent of control.
[b]Calculated by reviewer.
Significantly different from controls; *$p \leq 0.05$, ***$p \leq 0.001$.

3. Offspring developmental milestones

Anogenital distances at birth were similar between treated and control F_1 males and females and F_2 males. Mid-dose F_2 females had a significantly ($p \leq 0.01$) greater anogenital distance as compared to the controls (1.1 mm vs 1.0 mm). The percentage of pups with eyes open on day 15 was slightly (n.s.) less than the controls for the high-dose F_1 pups (79.2% vs 85.2% of the controls) and for the mid-dose F_2 pups (84.6% vs 96.9% of the controls). No differences were observed between treated and control litters of either generation for the percentage of pups with ears open on day 3, righting reflex on day 5, startle response on day 15, and pupillary light reflex on day 21.

4. Offspring postmortem results

a. Organ weights - Organ weights were not obtained from pups at necropsy.

b. Pathology

1. Macroscopic pathology

No treatment-related lesions were found in pups that were found dead or included in lactation day 4 culls. Gross necropsy of weanlings was unremarkable.

2. Microscopic pathology

Microscopic examinations of tissues from the pups were not conducted.

III. DISCUSSION

A. INVESTIGATOR'S CONCLUSIONS

The study author concluded that administration of Omacide® to rats over two generations resulted in systemic and reproductive toxicity. Administration of 100 mg/kg/day resulted in clinical signs of toxicity, reduction in male and female body weight gain, reduced food consumption by the males during the first week and females during lactation, and increased male liver weight and increased female ovary weight. Fertility indices were reduced at this dose level and the number of females sacrificed during parturition was increased. The number of pups with eyes open on day 15 and pup body weights were reduced compared to the control group. Also, the number of pups sacrificed or found dead was slightly increased with findings at necropsy consistent with lack of maternal care.

Toxicity at 30 mg/kg/day included clinical signs in both generations, reduced food consumption in F_1 males, increased ovary weights in the F_0 females, and thickening of the stomach lining of the F_1 animals. Also at this dose, pup survival indices were reduced in the F_1 generation, pup growth was reduced in both generations, and pup development was retarded in the F_2 generation.

Therefore, the author stated that the NOEL for systemic toxicity and reproductive toxicity was 10 mg/kg/day.

B. REVIEWER'S DISCUSSION

1. Systemic toxicity

Premature sacrifices of the mid- and high-dose F_0 females with dystocia are considered treatment-related, but the mechanism is unknown. Dose-related clinical signs of toxicity, such as paddling with the forepaws, salivation, and hunched posture immediately postdosing in the mid- and high-dose groups of both generations,

indicate that the test article may have been irritating to the animals. The slight reductions in body weight and body weight gain by the high-dose F_0 males may be due to treatment, but are of questionable biological significance. No other effects on body weights were observed in either sex of either generation during the premating interval. Reduced food consumption by the high-dose F_0 dams during lactation is considered treatment-related and is probably due to decreased survival of the pups, i.e., fewer pups required less nutritional maintenance by the dams.

At necropsy, increased relative liver weights from the high-dose F_0 males are probably a result of the slightly lower final body weights of these animals and not an indication of toxicity. Absolute liver weights were not increased in F_0 males or females at this dose and relative weights were not increased in the F_0 females. Thickening of the stomach lining in the 30 mg/kg/day F_1 animals supports the hypothesis that the chemical may have been irritating, which has been substantiated by other long-term studies with this chemical. Although this lesion was not reported for the F_0 adults, it is considered treatment-related in the F_1 adults because these animals were exposed for a longer period of time (through two pairings) and beginning at a younger age.

Therefore, the LOAEL for systemic toxicity is 30 mg/kg/day based on clinical signs of toxicity in the F_0 and F_1 males and females and on microscopic lesions in the stomach of F_1 males and females. The systemic toxicity NOAEL is 10 mg/kg/day.

2. Reproductive toxicity

Increased relative weights of the reproductive organs from the high-dose F_0 males are probably a result of the slightly lower final body weights of these animals and not an indication of toxicity. High-dose F_0 females had significantly greater absolute and relative ovary weights as compared to the controls, but the relationship to treatment is questionable. It is unfortunate that the effect of treatment on the increases in the absolute and/or relative weights of the reproductive organs of the high-dose F_0 animals could not be confirmed because this dose was not repeated in the F_1 animals, and in addition, decreases in ovarian weight were observed in this generation of females. No treatment-related effects were observed on estrous cycle length or periodicity or on sperm measures in adults of either generation. Endpoints of sexual maturation of the F_1 pups were similar between the treated and control groups.

Omacide® (IPBC) did not appear to affect the reproductive performance of animals given 10 or 30 mg/kg/day. However, male and female fertility indices were significantly reduced at 100 mg/kg/day. Significantly increased gestation length in all treated F_0 females may have been due to treatment in the mid- and high-dose groups, but not for the low-dose group. In the mid- and high-dose F_0 groups, an the length of gestation correlated with an increase in the number of dams sacrificed with dystocia. However, the effect was not repeated in the treated F_1 dams.

The main reproductive toxicity effect of the test article appeared to be on growth and survival of the pups. Viability indices of the mid- and high-dose F_1 pups were significantly reduced as compared to the controls with most deaths occurring between lactation days 0-4. Viability of the mid-dose F_2 litters was also slightly reduced on lactation day 4. Reduced body weights and body weight gains of the high-dose male and female F_1 pups and the mid-dose female F_2 pups were considered treatment-related even though the mid-dose F_1 females were not affected. The lower body weights of the F_2 females correlated with developmental delays observed as a lower percentage of pups with their eyes open on lactation day 15. Decreased pup survival, reduced pup growth, lack of maternal care, and developmental delays of the pups suggest a lactational effect of the test article. It is possible that either the quality or quantity of milk production was affected.

Therefore, the LOAEL for reproductive toxicity is 30 mg/kg/day based on reduced pup survival, lower pup body weights, and developmental delays during lactation. The reproductive toxicity NOAEL is 10 mg/kg/day.

C. STUDY DEFICIENCIES

Histopathological data for the F_o males was not included in the report, and summary data on sperm morphology and estrous cycling were not presented in the report, although individual animal data for sperm and estrous cycling parameters were shown in the report. However, these deficiencies are not expected to alter the conclusions of this review.

D. CORE CLASSIFICATION

This study is classified as **Acceptable (guideline)** and satisfies the guideline requirement for a reproduction study (OPPTS 870.3800; 40 CFR §83-4) in rats.

Signed-off 3/3/99 by Norm Cook
TXR# 1001077